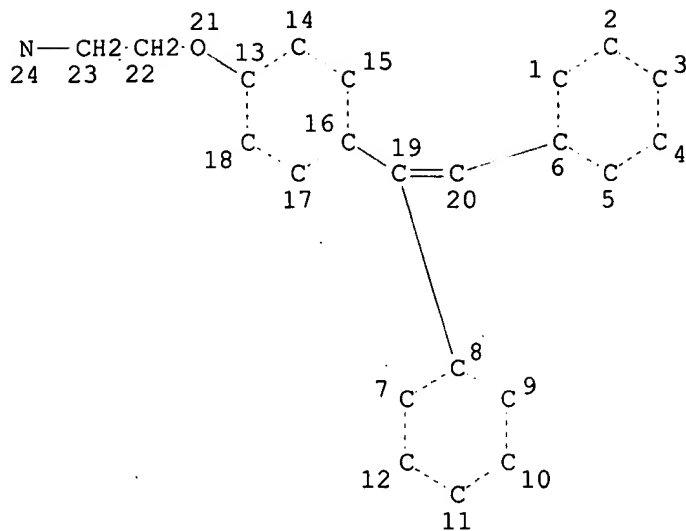


J. Kim
572926

=> d 13 que stat;e clc3 blocker/cn 5
L1 STR



NODE ATTRIBUTES:

NSPEC IS RC AT 24
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 24

STEREO ATTRIBUTES: NONE

L3 1593 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 1843 ITERATIONS
SEARCH TIME: 00.00.04

1593 ANSWERS

E1	1	CLC-D CHLORIDE CHANNEL (ARABIDOPSIS THALIANA STRAIN COLUMBIA CLONE MYF5)/CN
E2	1	CLC-K1 CHLORIDE CHANNEL (RAT KIDNEY HENLE'S LOOP ASCENDING L IMB CLONE CLC-K1)/CN
E3	0 -->	CLC3 BLOCKER/CN
E4	1	CLD/CN
E5	1	CLD 2/CN

=> e clc-3 blocker/cn 5

E1	1	CLC 756/CN
E2	1	CLC FAMILY, CHLORINE TRANSPORT PROTEIN (SALMONELLA ENTERICA TYPHIMURIUM STRAIN LT2; SGSC 1412; ATCC 700720 GENE YADQ)/CN
E3	0 -->	CLC-3 BLOCKER/CN
E4	1	CLC-355/CN
E5	1	CLC-D CHLORIDE CHANNEL (ARABIDOPSIS THALIANA STRAIN COLUMBIA CLONE MYF5)/CN

=> e clc 3/cn 5

E1	1	CLBPEA/CN
E2	1	CLC 201/CN
E3	0 -->	CLC 3/CN

Searched by: Mary Hale 308-4258 CM-1 1E01

E4 1 CLC 450/CN
E5 1 CLC 535/CN

=> fil medl,hcap,biosis,embase,jist

'JIST' IS NOT A VALID FILE NAME

Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files that are available. If you have requested multiple files, you can specify a corrected file name or you can enter "IGNORE" to continue accessing the remaining file names entered.

ENTER A FILE NAME OR (IGNORE):jicst

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	141.80	142.01

FILE 'MEDLINE' ENTERED AT 07:28:00 ON 24 JUL 2002

FILE 'HCAPLUS' ENTERED AT 07:28:00 ON 24 JUL 2002

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=> s l3 or clc3 blocker

L4 12665 FILE MEDLINE
L5 6694 FILE HCAPLUS
L6 13162 FILE BIOSIS
L7 22225 FILE EMBASE
L8 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES

L9 54746 L3 OR CLC3 BLOCKER

=> s l9 and (smooth muscle endothelium damage? or endothelium damage? or diabete? or hypertens? or blood pressure or coronary arter? disease? or coronary(a)arteriosclerosis or surger? or surgical procedure?)

L10 1283 FILE MEDLINE
L11 191 FILE HCAPLUS
L12 760 FILE BIOSIS
L13 3882 FILE EMBASE
L14 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES

L15 6116 L9 AND (SMOOTH MUSCLE ENDOTHELIUM DAMAGE? OR ENDOTHELIUM DAMAGE? OR DIABETE? OR HYPERTENS? OR BLOOD PRESSURE OR CORONARY ARTER? DISEASE? OR CORONARY(A) ARTERIOSCLEROSIS OR SURGER? OR SURGICAL PROCEDURE?)

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	135.18	277.19

FILE 'REGISTRY' ENTERED AT 07:33:04 ON 24 JUL 2002

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DICTIONARY FILE UPDATES: 22 JUL 2002 HIGHEST RN 439790-45-1

TSCA INFORMATION NOW CURRENT THROUGH January 7, 2002

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES
for more information. See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

```
=> e "1-p-.beta.-dimethylaminoethoxyphenyl-trans-1,2-diphenylbut-1-ene"/cn 5
E1      1      1-P-(METHYLSULFONYL)PHENYL-3-O-(ISOHEXADECYLOXY)PHENYL-2-PYR
          AZOLIN-5-ONE/CN
E2      1      1-P-(TOLYLOXY)-2,3-EPOXYPROPANE/CN
E3      0 --> 1-P-.BETA.-DIMETHYLAMINOETHOXYPHENYL-TRANS-1,2-DIPHENYLBUT-1
          -ENE/CN
E4      1      1-P-ACRYLOYLOXYPHENYL-4-PROPYLCYCLOHEXANE-1-(P-ACRYLOYLOXYPH
          ENYL)-2-(P'-PENTYLPHENYL)ACETYLENE COPOLYMER/CN
E5      1      1-P-AMINOPHENYL-1,2,4-TRIAZOLE/CN
```

```
=> e "1-p-b-dimethylaminoethoxyphenyl-trans-1,2-diphenylbut-1-ene"/cn 5
E1      1      1-P-ANISYLLYSERGOL/CN
E2      1      1-P-ANISYLPPIPERIDINE/CN
E3      0 --> 1-P-B-DIMETHYLAMINOETHOXYPHENYL-TRANS-1,2-DIPHENYLBUT-1-ENE/
          CN
E4      1      1-P-BENZOQUINONYL-1-PHENYLETHYLENE/CN
E5      1      1-P-BENZOQUINONYLAZIRIDINE/CN
```

```
=> e tamoxifen/cn 5
E1      1      TAMOTSU V/CN
E2      1      TAMOX-PUREN/CN
E3      1 --> TAMOXIFEN/CN
E4      2      TAMOXIFEN ALCOHOL/CN
E5      1      TAMOXIFEN AZIRIDINE/CN
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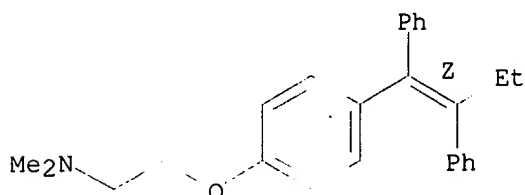
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=> s e3;d ide can
L16      1 TAMOXIFEN/CN
```

```
L16 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 10540-29-1 REGISTRY
CN Ethanamine, 2-[4-[(1Z)-1,2-diphenyl-1-butenyl]phenoxy]-N,N-dimethyl- (9CI)
  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)-
CN Ethylamine, 2-[p-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)-
  (8CI)
OTHER NAMES:
CN ICI 47699
CN Mammaton
CN Tamofen
CN Tamoxifen
CN trans-Tamoxifen
```

Searched by: Mary Hale 308-4258 CM-1 1E01

CN Z-Tamoxifen
 FS STEREOSEARCH
 MF C26 H29 N O
 CI COM
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
 BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS,
 CHEMINFORMRX, CHEMLIST, CIN, CSCHM, CSNB, DDFU, DIOGENES, DRUGNL,
 DRUGPAT, DRUGU, EMBASE, HSDB*, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR,
 PHARMASEARCH, PROMT, RTECS*, SPECINFO, TOXCENTER, ULIDAT, USAN, USPAT2,
 USPATFULL, VETU
 (*File contains numerically searchable property data)
 Other Sources: EINECS**, WHO
 (**Enter CHEMLIST File for up-to-date regulatory information)

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4424 REFERENCES IN FILE CA (1967 TO DATE)
 127 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 4437 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 137:47211
 REFERENCE 2: 137:43602
 REFERENCE 3: 137:42862
 REFERENCE 4: 137:42577
 REFERENCE 5: 137:42095
 REFERENCE 6: 137:41724
 REFERENCE 7: 137:41390
 REFERENCE 8: 137:41253
 REFERENCE 9: 137:41076
 REFERENCE 10: 137:37765

=> fil medl,hcap,biosis,embase,jicst
 COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
7.68	284.87

FULL ESTIMATED COST

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=> s l15 and (ameliorate or reduc?(5a)sensit? or negative effect!)

L17	3 FILE MEDLINE
L18	1 FILE HCAPLUS
L19	0 FILE BIOSIS
L20	7 FILE EMBASE
L21	0 FILE JICST-EPLUS

TOTAL FOR ALL FILES

L22	11 L15 AND (AMELIORATE OR REDUC?(5A) SENSIT? OR NEGATIVE EFFECT!)
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=> dup rem l22
PROCESSING COMPLETED FOR L22

L23	9 DUP REM L22 (2 DUPLICATES REMOVED)
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=> d cbib abs 1-9

L23	ANSWER 1 OF 9	MEDLINE	DUPLICATE 1
2002291502 Document Number: 22027518. PubMed ID: 12032379. Optimizing ovulation induction in women with polycystic ovary syndrome. Seli Emre; Duleba Antoni J. (Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut, USA.) CURRENT OPINION IN OBSTETRICS AND GYNECOLOGY, (2002 Jun) 14 (3) 245-54. Ref: 61. Journal code: 9007264. ISSN: 1040-872X. Pub. country: England: United Kingdom. Language: English.			

AB Recent developments in our understanding of the pathophysiology of polycystic ovary syndrome led to the introduction of new therapeutic approaches. It is apparent that a significant proportion of women with polycystic ovary syndrome have insulin resistance and compensatory hyperinsulinemia. Growing evidence indicates that elevated serum insulin induces hyperandrogenism, which in turn leads to anovulation and infertility. Hyperinsulinemia also contributes to the increased risk for cardiovascular disorders and type 2 **diabetes** mellitus. These concepts provide rationale for therapies focused on treatments of insulin resistance. In particular, weight loss and exercise have been shown to increase insulin sensitivity and improve ovulatory function. Metformin, an insulin-sensitizing agent, is particularly effective in women with polycystic ovary syndrome who have significant insulin resistance. Metformin use leads to a decrease in serum insulin and androgen levels as well as an improvement in ovulatory function. Moreover, it appears to **ameliorate** cardiovascular risk factors. Other approaches to ovulation induction in women with polycystic ovary syndrome include traditional therapies using clomiphene citrate or gonadotropins. In clomiphene-resistant subjects, one can consider laparoscopic ovarian drilling and other forms of partial ovarian resection or destruction.

L23	ANSWER 2 OF 9	MEDLINE
2002217380 Document Number: 21951114. PubMed ID: 11953071. Effects of metformin on the plasminogen activator system, endocrine, metabolic		

Searched by: Mary Hale 308-4258 CM-1 1E01

profiles in patients with polycystic ovary syndrome and clomiphene resistant cases. Song Juxiang; Shen Hongmin; Li Jianye; Huang Zhenguo; Zhang Yuhua. (Department of Obstetrics and Gynecology, People's Hospital of Shanxi Province, Taiyuan 030001, China.) CHUNG-HUA FU CHAN KO TSA CHIH [CHINESE JOURNAL OF OBSTETRICS AND GYNECOLOGY], (2002 Feb) 37 (2) 86-9. Journal code: 16210370R. ISSN: 0529-567X. Pub. country: China. Language: Chinese.

AB OBJECTIVE: To assess the therapeutic effects of metformin in patients with polycystic ovary syndrome (PCOS) and clomiphene (CC) resistant cases. METHODS: Thirty one patients with PCOS, including 8 CC resistant cases were studied. Serum tissue-type plasminogen activator (tPA), plasminogen activator inhibitor type 1 (PAI-1), menstrual and reproductive hormone patterns, lipid and glucose metabolic parameters, bilateral ovarian volume, side effects were determined before and after oral administration of metformin 375 mg three times daily for 12 - 16 weeks. Metformin and CC were co-administered in CC resistant cases who had not restored their menstrual cycle after the treatment with metformin alone for investigating ovulation rate. In the remaining non-CC resistant metformin failure cases the dosage of metformin was increased to 500 mg three times daily for investigating menstrual cycle. RESULTS: After administration of metformin for 12 - 16 weeks, serum PAI-1, luteinizing hormone (LH)/follicle stimulating hormone (FSH) ratio, androstenedione, testosterone, low density lipoprotein-cholesterol, total cholesterol, fasting insulin concentration and response to oral glucose tolerant test (OGTT), diastolic **blood pressure** decreased significantly, while FSH and estradiol levels increased, bilateral ovarian volume shrunk significantly ($P < 0.05 - 0.01$). Body mass index, waist hip ratio, LH, tPA, systolic **blood pressure**, prolactin, fasting glucose concentration and response to OGTT, high density lipoprotein-cholesterol, apolipoprotein A, apolipoprotein B, triglycerides levels did not change significantly ($P > 0.05$). Nineteen out of thirty one cases (61%) had restoration of menstrual cycle, 2 became pregnant. In 6 CC resistant cases who had not restoration of menstrual cycle after the treatment with metformin, CC induced ovulation in 12/18 cycles or 5/6 cases and 2 pregnancies achieved. In others 6 metformin failure cases the dosage of metformin was increased to 500 mg three times daily, one restored menstrual cycle and became pregnant. CONCLUSIONS: Metformin may **ameliorate** the PAI-1, endocrine, metabolic profiles and menstrual abnormalities and improve the ovarian response to CC in CC resistant cases. Metformin provides a safe and effective approach to the treatment of PCOS.

L23 ANSWER 3 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2001208786 EMBASE Metformin and intervention in polycystic ovary syndrome. Norman R.J.; Kidson W.J.; Cuneo R.C.; Zacharin M.R.. Prof. Dr. R.C. Cuneo, Department of Medicine, Princess Alexandra Hospital, Brisbane, QLD 4102, Australia. Medical Journal of Australia 174/11 (580-583) 4 Jun 2001. Refs: 33. ISSN: 0025-729X. CODEN: MJAUAJ. Pub. Country: Australia. Language: English. Summary Language: English.

AB Polycystic ovary syndrome (PCOS) is classically characterised by ovarian dysfunction (oligomenorrhoea, anovulation and infertility), androgen excess (hirsutism and acne), obesity, and morphological abnormalities of the ovaries (cystic enlargement and stromal expansion). More recently, insulin resistance has been found to be common in PCOS, along with an increased prevalence of other features of the "metabolic syndrome", namely glucose intolerance, type 2 **diabetes** mellitus, and hyperlipidaemia. Hyperinsulinaemia is likely to contribute to the disordered ovarian function and androgen excess of PCOS. Reducing insulin resistance by lifestyle modifications such as diet and exercise improves endocrine and menstrual function in PCOS. These lifestyle modifications are the best initial means of improving insulin resistance. Metformin, an oral hypoglycaemic agent that increases insulin **sensitivity**, has

been shown to **reduce** serum concentrations of insulin and androgens, to reduce hirsutism, and to improve ovulation rates. The effect of metformin alone on fertility rates is unknown. Some studies suggest that metformin will reduce total body weight to a small extent, but with a predominant effect on visceral adipose reduction. The effects of metformin on lipid abnormalities, **hypertension** or premature vascular disease are unknown, but the relative safety, moderate cost, and efficacy in reducing insulin resistance suggest that metformin may prove to be of benefit in combating these components of the "metabolic" syndrome in PCOS. Further properly planned randomised controlled trials are required.

L23 ANSWER 4 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2001127569 EMBASE In-office and intraoperative sonohysterography:

Indications, applications, and interpretations. Letterie G.S.. Dr. G.S. Letterie, Center for Fertility/Reprod. Endoc., Virginia Mason Medical Center, 1100 Ninth Avenue FC-11, Seattle, WA 98110, United States.

Reproductive Technologies 10/5 (233-243) 2001.

Refs: 68.

ISSN: 1528-4840. CODEN: RTEEBF. Pub. Country: Canada. Language: English.

Summary Language: English.

AB Ultrasound imaging of the uterus has progressed from imprecise B-mode through real-time transabdominal techniques to highly sensitive two- and three-dimensional transvaginal imaging. The results of these improvements have been increased **sensitivity** and ease of use at **reduced** cost. Saline infusion sonohysterography is a technique for enhanced transvaginal and, in select circumstances, transabdominal ultrasonographic examination of the uterine cavity. Sonohysterography may be performed as either an in-office or as an intraoperative procedure. In-office saline sonohysterography is a noninvasive and cost-effective method of assessing the endometrial cavity for abnormalities such as endometrial polyps, submucous fibroids, and intrauterine adhesions in gynecologic, infertility, and perimenopausal patients. It is a less costly and less invasive procedure than hysteroscopy with equal sensitivities and specificities. In-office sonohysterography is the preferred procedure for assessing clinical integrity of the endometrial cavity and the need for more invasive procedures such as office hysteroscopy, endometrial biopsy, or dilation and curettage. Intraoperative sonohysterography using both transabdominal and laparoscopic ultrasound probes offers improved visualization during intrauterine procedures and a potential role in limiting the need for laparoscopic guidance of complex intrauterine procedures. Studies are limited, however. Intraoperative sonohysterography may prove to be an equally efficacious and more cost-effective approach than laparoscopy when intraoperative guidance for hysteroscopic **surgery** is required. The purpose of this report is to review the indications and techniques of sonohysterography as both an in-office procedure and as an intraoperative adjunct during endoscopic **surgery** and the clinical settings in which it is most useful.

L23 ANSWER 5 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2001253339 EMBASE Use of antidepressants in treatment of comorbid

diabetes mellitus and depression as well as in diabetic neuropathy. Goodnick P.J.. Dr. P.J. Goodnick, Department of Psychiatry, Univ. of Miami School of Medicine, 1400 NW 10 Avenue, Miami, FL 33136, United States. goodnick@aol.com. Annals of Clinical Psychiatry 13/1 (31-41) 2001.

Refs: 83.

ISSN: 1040-1237. CODEN: APSYEZ. Pub. Country: United States. Language: English. Summary Language: English.

AB After a brief review of epidemiology, the focus is on biochemistry of **diabetes**. Animal and human studies are reviewed in terms of the impact of alterations in catecholamines and serotonin (5-hydroxytryptamine, 5HT) on glucose utilization. Then, the implications of

these experimental results for the choice of antidepressant in comorbid **diabetes** mellitus and depression as well as in diabetic neuropathy are discussed. Results of clinical investigations are then reviewed in terms of the above hypotheses. An Index Medicus Search for the past 10 years was supplemented by references from previous related reviews of the topic as well as by pending results, where available, not previously published. The range of prevalence of depression in diabetic patients has been 8-27%, depending on study criteria and procedures. An increase of catecholamines appears to increase glucose while both **reducing** insulin release and **reducing sensitivity** to insulin that is available. In contrast, increases in serotonergic function by increased precursor, increased release, or blocked metabolism and blocked reuptake in contrast seem to increase **sensitivity** to insulin and **reduce** plasma glucose. There have been six studies of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), at a dose of 60 mg/day pursued up to 12 months that have demonstrated that medication's usefulness in diabetic patients, with reductions in weight (to 9.3 kg), in FPG (to 45 mg%), and in HbA1c (to 2.5%). In studies in comorbid **diabetes** mellitus and depression, nortriptyline, a norepinephrine reuptake inhibitor that produces increased synaptic catechols, has led to worsening of indices of glucose control. However, fluoxetine and sertraline, both selective serotonin reuptake inhibitors, in the same patient group, have produced results consistent with reductions in glucose levels. In diabetic neuropathy, perhaps due to the fact that catecholamines and serotonin may both be implicated in pain pathways, dual-action antidepressants appear more effective at lower doses than do specific serotonergic agents. The tricyclic antidepressants (TCA) (66.7%) have had success in double-blind studies, particularly imipramine, with a 81% response rate. Yet, there are positive reports concerning the SSRIs (paroxetine, citalopram, sertraline), as well as nefazodone, that focus on serotonin selectivity. Conclusions: In comorbid **diabetes** mellitus and depression, most evidence supports the use of fluoxetine in control of glucose handling. Other characteristics in terms dosing, drug interactions, cognition, and sleep make sertraline an attractive alternative agent. In diabetic neuropathy without depression, the best choices among non-TCA's may include sertraline, citalopram, and perhaps, venlafaxine, since the TCAs appear to increase cravings and increase FBG levels.

L23 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2002 ACS

20000608566 Document No. 133:172188 Methods to **reduce** the **sensitivity** of endothelially-compromised vascular smooth muscle.

Lamb, Fred S. (University of Iowa Research Foundation, USA). PCT Int. Appl. WO 2000050023 A2 20000831, 34 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US4892 20000226. PRIORITY: US 1999-PV121727 19990226.

AB The present invention discloses materials and methods useful to treat sensitivity of endothelially-compromised vascular smooth muscle. In one embodiment, **CLC3 blockers**, particularly compds. of formula I are used to treat sensitivity.

L23 ANSWER 7 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

20000315842 EMBASE Ovulation induction for polycystic ovary syndrome. Balen A.. A. Balen, Department of Reproductive Medicine, General Infirmary, Leeds LS2 9NS, United Kingdom. Human Fertility 3/2 (106-111) 2000.

Refs: 61.

ISSN: 1464-7273. CODEN: HUMFFR. Pub. Country: United Kingdom. Language: English. Summary Language: English.

- AB Polycystic ovary syndrome (PCOS) is the commonest cause of anovulatory infertility. Various factors influence ovarian function, and fertility is adversely affected by an individual being overweight or having high serum concentrations of LH. Strategies to induce ovulation include weight loss, oral anti-oestrogens (principally clomiphene citrate), parenteral gonadotrophin therapy and laparoscopic ovarian **surgery**. There have been no adequately powered randomized studies to determine which of these therapies provides the best overall chance of an ongoing pregnancy. Women with PCOS are at risk of ovarian hyperstimulation syndrome (OHSS) and so ovulation induction has to be monitored carefully with serial ultrasound scans. The recognition of an association between hyperinsulinaemia and PCOS has resulted in the use of insulin sensitizing agents, such as metformin, which appear to **ameliorate** the biochemical profile and improve reproductive function.

L23 ANSWER 8 OF 9 MEDLINE

DUPLICATE 2

1999281705 Document Number: 99281705. PubMed ID: 10355574. Combined sequential approach in locally advanced breast cancer. Zambetti M; Oriana S; Quattrone P; Verderio P; Terenziani M; Zucali R; Valagussa P; Bonadonna G. (Istituto Nazionale Tumori, Milano, Italy.) ANNALS OF ONCOLOGY, (1999 Mar) 10 (3) 305-10. Journal code: 9007735. ISSN: 0923-7534. Pub. country: Netherlands. Language: English.

- AB BACKGROUND: The interaction between primary and adjuvant chemotherapy is a crucial point in the treatment of locally advanced breast cancer. OBJECTIVE: To evaluate the therapeutic efficacy of a sequential treatment with primary anthracyclines and adjuvant CMF in this patient subset. DESIGN: Prospective cohort study. PATIENTS: Eighty-eight breast cancer patients, stage T3b-T4 abc, N0-2, M0. RESULTS: From February 1991 to July 1994, 88 consecutive patients with locally advanced breast cancer were treated at the Istituto Nazionale Tumori, Milano, with full-dose doxorubicin (75 mg/m²) or epirubicin (120 mg/m²) for three cycles followed by **surgery**, adjuvant chemotherapy with i.v. CMF for six cycles and local radiotherapy +/- Tamoxifen. A high rate of objective responses (70%), but a low incidence of pathologic complete remission (2%), were observed following primary treatment with single-agent anthracyclines. Frequency of responses was not associated with tumor estrogen or progesterone receptors status, Mib-1 or grading. In 28 patients (32%) conservative **surgery** could be performed. At a median follow-up of 52 months, relapse free survival and overall survival are 52% and 62%, respectively. A multivariate analysis demonstrated a significant favorable prognosis in patients with limited nodal involvement at **surgery** and negative Mib-1 values. This drug sequence failed to significantly **ameliorate** the long term results in this unfavorable patient subset and more effective drug regimens and innovative therapeutic strategies are needed.

L23 ANSWER 9 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

95366442 EMBASE Document No.: 1995366442. Alternate usages for medications update. Elia J.C.. 1680 Circle Way, Reno, NV 89509, United States. Journal of Neurological and Orthopaedic Medicine and Surgery 16/3 (167-172) 1995.

ISSN: 0890-6599. CODEN: JOMSEB. Pub. Country: United States. Language: English. Summary Language: English.

- AB The item of alternate usages of medications is becoming very important these days. An example is the use of colchicine, the ancient gout medication, for disk disease and to **ameliorate** multiple sclerosis. I believe we are remiss if information on alternate usages of medications is not made available to all clinicians on the front line of the practice of medicine and **surgery** in America. The original

material of the following report was published in abridged form in the October 1987 issue of this journal [1], and some of the work was presented at the 11th Annual Meeting of our academy, October 23rd, 1987, but a more embellished form of this noteworthy material is submitted at this time.

```
=> s lamb, f?/au,in
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L24      63 FILE MEDLINE
L25      191 FILE HCAPLUS
L26      85 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L27      52 FILE EMBASE
L28      2 FILE JICST-EPLUS
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```
TOTAL FOR ALL FILES
L29      393 LAMB, F?/AU,IN
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L30      0 FILE MEDLINE
L31      2 FILE HCAPLUS
L32      3 FILE BIOSIS
L33      0 FILE EMBASE
L34      0 FILE JICST-EPLUS
```

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TOTAL FOR ALL FILES
L35      5 L29 AND L9
```

```
=> s l35 not l22
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L37      1 FILE HCAPLUS
L38      3 FILE BIOSIS
L39      0 FILE EMBASE
L40      0 FILE JICST-EPLUS
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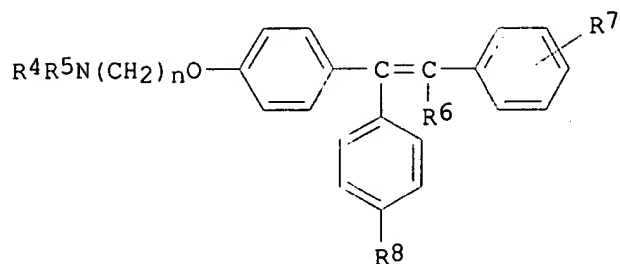
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TOTAL FOR ALL FILES
L41      4 L35 NOT L22
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```
=> dup rem l41
PROCESSING COMPLETED FOR L41
L42      4 DUP REM L41 (0 DUPLICATES REMOVED)
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=> d cbib abs 1-4
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L42 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2002 ACS
2002:409273 Document No. 137:722 Use of CLC3 chloride channel blockers to
modulate vascular tone. Lamb, Fred S.; Schutte, Brian C.; Yang,
Baoli (USA). U.S. Pat. Appl. Publ. US 20020065325 A1 20020530, 46 pp.,
Cont.-in-part of U. S. Ser. No. 512,926. (English). CODEN: USXXCO.
APPLICATION: US 2001-930105 20010815. PRIORITY: US 1999-PV121727
19990226; US 2000-512926 20000225.
```

GI



AB The invention discloses the use of chloride channel blocking compd. I (R4= H, lower alkyl radical; R5= lower alkyl radical; or R4 and R5 connected with adjacent nitrogen to form a heterocyclic radical; R6= H, lower alkyl radical; R7=H, halogen, OH, lower alkyl radical, buta-1-3-dienyl radical which together with adjacent Ph forms a naphthyl radical; R8=H, OH; n=2) for the modulation of vascular tone in a patient having compromised vascular tissue. The present invention also provides methods for the modulation of vascular tone in a patient having compromised vascular tissue, with the administration of a chloride channel blocking agent or a pharmaceutically acceptable salt thereof.

L42 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

2000:275151 Document No.: PREV200000275151. Endothelium modulates anion channel-dependent aortic contractions to iodide. **Lamb, Fred S. (1)** ; Barna, Thomas J.. (1) Dept. of Pediatrics, 5040-B RCP Univ. of Iowa Hospitals, Iowa City, IA, 52242 USA. American Journal of Physiology, (May, 2000) Vol. 278, No. 5 part 2, pp. H1527-H1536. print.. ISSN: 0002-9513. Language: English. Summary Language: English.

AB Anion currents contribute to vascular smooth muscle (VSM) membrane potential. The substitution of extracellular chloride (Cl) with iodide (I) or bromide (Br) initially inhibited and then potentiated isometric contractile responses of rat aortic rings to norepinephrine. Anion substitution alone produced a small relaxation, which occurred despite a lack of active tone and minimal subsequent contraction of endothelium-intact rings (4.2 +/- 1.2% of the response to 90 mM KCl). Endothelium-denuded rings underwent a similar initial relaxation but then contracted vigorously (I > Br). Responses to 130 mM I (93.7 +/- 1.9% of 90 mM KCl) were inhibited by nifedipine (10⁻⁶ M), niflumic acid (10⁻⁵ M), tamoxifen (10⁻⁵ M), DIDS (10⁻⁴ M), and HCO₃--free buffer (HEPES 10 mM) but not by bumetanide (10⁻⁵ M). Intact rings treated with Nomega-nitro-L-arginine (10⁻⁴ M) responded weakly to I (15.5 +/- 2.1% of 90 mM KCl), whereas hemoglobin (10⁻⁵ M), indomethacin (10⁻⁶ M), 17-octadecynoic acid (10⁻⁵ M), and 1H-(1,2,4)oxadiazole(4,3-a)quinoxalin-1-one (10⁻⁶ M) all failed to augment the response of intact rings to I. We hypothesize that VSM takes up I primarily via an anion exchanger. Subsequent I efflux through anion channels having a selectivity of I > Br > Cl produces depolarization. In endothelium-denuded or agonist-stimulated vessels, this current is sufficient to activate voltage-dependent calcium channels and cause contraction. Neither nitric oxide nor prostaglandins are the primary endothelial modulator of these anion channels. If they are regulated by an endothelium-dependent hyperpolarizing factor it is not a cytochrome P-450 metabolite.

L42 ANSWER 3 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

1999:170544 Document No.: PREV199900170544. Tamoxifen normalizes the increase in vascular sensitivity associated with endothelial disruption. Liu, B.-X.; Barna, T. J.; **Lamb, F. S.** Univ. Iowa Pediatr., Iowa City, IA 52242 USA. FASEB Journal, (March 12, 1999) Vol. 13, No. 4 PART 1, pp. A59. Meeting Info.: Annual Meeting of the Professional Research

Scientists for Experimental Biology 99 Washington, D.C., USA April 17-21,
1999 ISSN: 0892-6638. Language: English.

L42 ANSWER 4 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

1998:387832 Document No.: PREV199800387832. Chloride ion currents contribute functionally to norepinephrine-induced vascular contraction. **Lamb, Fred S. (1)**; Barna, Thomas J.. (1) Dep. Pediatr., 5040C RCP, Univ. Iowa Hosp., Iowa City, IA 52242 USA. American Journal of Physiology, (July, 1998) Vol. 275, No. 1 PART 2, pp. H151-H160. ISSN: 0002-9513. Language: English.

AB Norepinephrine (NE) increases Cl⁻ efflux from vascular smooth muscle (VSM) cells. An increase in Cl⁻ conductance produces membrane depolarization. We hypothesized that if Cl⁻ currents are important for agonist-induced depolarization, then interfering with cellular Cl⁻ handling should alter contractility. Isometric contraction of rat aortic rings was studied in a bicarbonate buffer. Substitution of extracellular Cl⁻ with 130 mM methanesulfonate (MS; 8 mM Cl⁻) did not cause contraction. NE- and serotonin- induced contractions were potentiated in this low-Cl⁻ buffer, whereas responses to K⁺, BAY K 8644, or NE in the absence of Ca²⁺ were unaltered. Substitution of Cl⁻ with or Br⁻ suppressed responses to NE. Inhibition of Cl⁻ transport with bumetanide (10⁻⁵ M) or bicarbonate-free conditions (10 mM HEPES) inhibited NE- but not KCl-induced contraction. The Cl⁻-channel blockers DIDS (10⁻³ M), anthracene-9-carboxylic acid (10⁻³ M), and niflumic acid (10⁻⁵ M) all inhibited NE-induced contraction, whereas tamoxifen (10⁻⁵ M) did not. Finally, disruption of sarcoplasmic reticular function with cyclopiazonic acid (10⁻⁷ M) or ryanodine (10⁻⁵ M) prevented the increase in the peak response to NE produced by low-Cl⁻ buffer. We conclude that a Cl⁻ current with a permeability sequence of I⁻ > Br⁻ > Cl⁻ > MS is critical to agonist-induced contraction of VSM.

=> s (l9 or l16 or 10540-29-1 or tamoxifen) and l29

L43 2 FILE MEDLINE
L44 4 FILE HCAPLUS
L45 3 FILE BIOSIS
L46 2 FILE EMBASE
L47 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES

L48 11 (L9 OR L16 OR 10540-29-1 OR TAMOXIFEN) AND L29

=> s l48 not (l22 or l35)

L49 2 FILE MEDLINE
L50 2 FILE HCAPLUS
L51 0 FILE BIOSIS
L52 2 FILE EMBASE
L53 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES

L54 6 L48 NOT (L22 OR L35)

=> dup rem l54

PROCESSING COMPLETED FOR L54

L55 2 DUP REM L54 (4 DUPLICATES REMOVED)

=> d l-2 cbib abs

L55 ANSWER 1 OF 2

MEDLINE

DUPLICATE 1

2000238189 Document Number: 20238189. PubMed ID: 10775130. Endothelium modulates anion channel-dependent aortic contractions to iodide. **Lamb F S**; Barna T J. (Department of Pediatrics, University of Iowa, Iowa City, Iowa 52242, USA.. fred-lamb@uiowa.edu) . AMERICAN JOURNAL OF

Searched by: Mary Hale 308-4258 CM-1 1E01

PHYSIOLOGY. HEART AND CIRCULATORY PHYSIOLOGY, (2000 May) 278 (5) H1527-36.
Journal code: 100901228. ISSN: 0363-6135. Pub. country: United States.
Language: English.

- AB Anion currents contribute to vascular smooth muscle (VSM) membrane potential. The substitution of extracellular chloride (Cl) with iodide (I) or bromide (Br) initially inhibited and then potentiated isometric contractile responses of rat aortic rings to norepinephrine. Anion substitution alone produced a small relaxation, which occurred despite a lack of active tone and minimal subsequent contraction of endothelium-intact rings (4.2 +/- 1.2% of the response to 90 mM KCl). Endothelium-denuded rings underwent a similar initial relaxation but then contracted vigorously (I > Br). Responses to 130 mM I (93.7 +/- 1.9% of 90 mM KCl) were inhibited by nifedipine (10(-6) M), niflumic acid (10(-5) M), **tamoxifen** (10(-5) M), DIDS (10(-4) M), and HCO(-)(3)-free buffer (HEPES 10 mM) but not by bumetanide (10(-5) M). Intact rings treated with N(omega)-nitro-L-arginine (10(-4) M) responded weakly to I (15.5 +/- 2.1% of 90 mM KCl), whereas hemoglobin (10(-5) M), indomethacin (10(-6) M), 17-octadecynoic acid (10(-5) M), and 1H-[1,2, 4]oxadiazole[4,3-a]quinoxalin-1-one (10(-6) M) all failed to augment the response of intact rings to I. We hypothesize that VSM takes up I primarily via an anion exchanger. Subsequent I efflux through anion channels having a selectivity of I > Br > Cl produces depolarization. In endothelium-denuded or agonist-stimulated vessels, this current is sufficient to activate voltage-dependent calcium channels and cause contraction. Neither nitric oxide nor prostaglandins are the primary endothelial modulator of these anion channels. If they are regulated by an endothelium-dependent hyperpolarizing factor it is not a cytochrome P-450 metabolite.

L55 ANSWER 2 OF 2 MEDLINE DUPLICATE 2
1998355830 Document Number: 98355830. PubMed ID: 9688908. Chloride ion currents contribute functionally to norepinephrine-induced vascular contraction. **Lamb F S**; Barna T J. (Department of Pediatrics, University of Iowa, Iowa City, Iowa, 52242, USA.) AMERICAN JOURNAL OF PHYSIOLOGY, (1998 Jul) 275 (1 Pt 2) H151-60. Journal code: 0370511. ISSN: 0002-9513. Pub. country: United States. Language: English.

- AB Norepinephrine (NE) increases Cl- efflux from vascular smooth muscle (VSM) cells. An increase in Cl- conductance produces membrane depolarization. We hypothesized that if Cl- currents are important for agonist-induced depolarization, then interfering with cellular Cl- handling should alter contractility. Isometric contraction of rat aortic rings was studied in a bicarbonate buffer. Substitution of extracellular Cl- with 130 mM methanesulfonate (MS; 8 mM Cl-) did not cause contraction. NE- and serotonin-induced contractions were potentiated in this low-Cl- buffer, whereas responses to K+, BAY K 8644, or NE in the absence of Ca2+ were unaltered. Substitution of Cl- with I- or Br- suppressed responses to NE. Inhibition of Cl- transport with bumetanide (10(-5) M) or bicarbonate-free conditions (10 mM HEPES) inhibited NE- but not KCl-induced contraction. The Cl--channel blockers DIDS (10(-3) M), anthracene-9-carboxylic acid (10(-3) M), and niflumic acid (10(-5) M) all inhibited NE-induced contraction, whereas **tamoxifen** (10(-5) M) did not. Finally, disruption of sarcoplasmic reticular function with cyclopiazonic acid (10(-7) M) or ryanodine (10(-5) M) prevented the increase in the peak response to NE produced by low-Cl- buffer. We conclude that a Cl- current with a permeability sequence of I- > Br- > Cl- > MS is critical to agonist-induced contraction of VSM.

=> s (19 or 116 or 10540-29-1 or tamoxifen) and (smooth muscle or endothelium damage?)

L56 83 FILE MEDLINE
L57 80 FILE HCAPLUS
L58 96 FILE BIOSIS

Searched by: Mary Hale 308-4258 CM-1 1E01

L59 117 FILE EMBASE
L60 5 FILE JICST-EPLUS

TOTAL FOR ALL FILES

L61 381 (L9 OR L16 OR 10540-29-1 OR TAMOXIFEN) AND (SMOOTH MUSCLE OR
ENDOTHELIUM DAMAGE?)

=> s l61 and (diabete? or hypertens? or blood pressure or coronary arter? disease?
or coronary(a)arteriosclerosis or surger? or surgical procedure?)

L62 4 FILE MEDLINE
L63 9 FILE HCAPLUS
L64 3 FILE BIOSIS
L65 15 FILE EMBASE
L66 1 FILE JICST-EPLUS

TOTAL FOR ALL FILES

L67 32 L61 AND (DIABETE? OR HYPERTENS? OR BLOOD PRESSURE OR CORONARY
ARTER? DISEASE? OR CORONARY(A) ARTERIOSCLEROSIS OR SURGER? OR
SURGICAL PROCEDURE?)

=> s l67 not (l22 or l35 or l48)

L68 4 FILE MEDLINE
L69 7 FILE HCAPLUS
L70 3 FILE BIOSIS
L71 15 FILE EMBASE
L72 1 FILE JICST-EPLUS

TOTAL FOR ALL FILES

L73 30 L67 NOT (L22 OR L35 OR L48)

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PROCESSING COMPLETED FOR L73

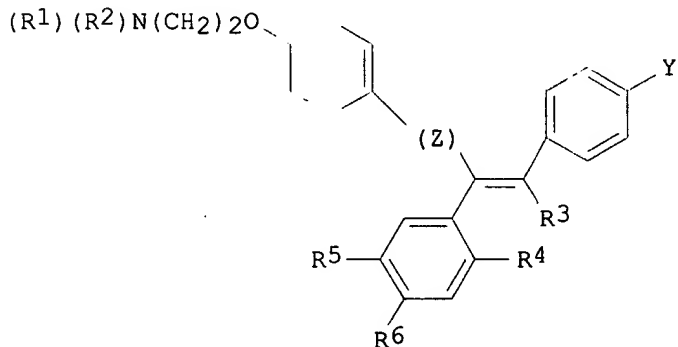
L74 25 DUP REM L73 (5 DUPLICATES REMOVED)

=> d 1-25 cbib abs

L74 ANSWER 1 OF 25 HCAPLUS COPYRIGHT 2002 ACS

2001:161506 Document No. 134:202697 Prevention and treatment of
cardiovascular pathologies with **tamoxifen** analogues. Grainger,
David J.; Metcalfe, James C.; Kunz, Lawrence L.; Schroff, Robert W. (NeoRx
Corporation, USA). U.S. US 6197789 B1 20010306, 48 pp., Cont.-in-part of
U.S. Ser. No. 478,936, abandoned. (English). CODEN: USXXAM.
APPLICATION: US 1997-973570 19971205. PRIORITY: US 1995-478936 19950607;
US 1995-476735 19950607; US 1995-477393 19950607; US 1995-486334 19950607;
WO 1996-US10211 19960607.

GI



AB A method for treating or preventing cardiovascular pathologies by administering a compd. of the formula (I): wherein Z is C:O or a covalent bond; Y is H or O(C1-C4)alkyl, R1 and R2 are individually (C1 -C4)alkyl or together with N are a satd. heterocyclic group, R3 is Et or chloroethyl, R4 is H, R5 is I, O(C1 -C4)alkyl or H and R6 is I, O(C1 -C4)alkyl or H with the proviso that when R4, R5, and R6 are H, R3 is not ethyl; or a pharmaceutically acceptable salt thereof, effective to elevate the level of TGF-beta to treat and/or prevent conditions such as atherosclerosis, thrombosis, myocardial infarction, and stroke is provided. Useful compds. include idoxifene, toremifene or salts thereof. Further provided is a method for identifying an agent that elevates the level of TGF-beta. Another embodiment of the invention is an assay or kit to det. TGF-beta in vitro. Also provided is a therapeutic method comprising inhibiting **smooth muscle** cell proliferation assocd. with procedural vascular trauma employing the administration of **tamoxifen** or structural analogs thereof, including compds. of formula (I).

L74 ANSWER 2 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

2001:257175 Document No.: PREV200100257175. Tyrosine hydroxylase (TH) enzyme activity and adrenomedullin (AdM) level in ovariectomized rat tissues depend on **tamoxifen**. Dogru, Mehmet Ilker (1); Yurekli, Muhittin (1); Kocagun, Arzu (1); Gokdeniz, Remzi (1). (1) Arts and Science Faculty, Biology Department, Inonu University, Malatya, 44069 Turkey. FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1170. print. Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001 ISSN: 0892-6638 Language: English. Summary Language: English.

AB The purpose of the present study was to investigate the effect of **tamoxifen** treatment on TH enzyme activity and adrenomedullin level in ovariectomized rats. Adrenomedullin (AdM) is a novel peptide that elicits a long-lasting vasorelaxant activity. It is expressed in several tissues including adrenal medulla, heart, lung, kidneys and cultured vascular **smooth muscle** cells. **Tamoxifen** is a medication in pill form. **Tamoxifen** has been used to treat patients with advanced breast cancer. While **tamoxifen** acts against the effects of estrogen in breast tissue, it acts like estrogen in other body systems. TH is the rate-limiting enzymatic step in the catecholamine biosynthesis pathway. Physiological stress, **hypertension**, aging, neurochemical alterations are well known to increase TH enzyme activity. TH activity was measured using a radioenzymatic assay. Reverse phase high pressure liquid chromatography was used for adrenomedullin measurement. In this study, TH enzyme activity was determined in hypothalamus and adrenal medulla and adrenomedullin level was measured in uterus. The results indicate that TH enzyme activity increased in hypothalamus and adrenal medulla and AdM level increased in uterus compared to control group.

L74 ANSWER 3 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2001433284 EMBASE Lymphangioleiomyomatosis: A series of three case reports illustrating the link with high oestrogen states. Wilson A.M.; Slack H.L.; Soosay S.A.; Taylor T.; Carey F.A.; Grove A.; Brown P.H.; Winter J.H.. Dr. A.M. Wilson, Department of Respiratory Medicine, Kings Cross Hospital, Dundee, United Kingdom. Scottish Medical Journal 46/5 (150-152) 2001. Refs: 11. ISSN: 0036-9330. CODEN: SMDJAK. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Lymphangioleiomyomatosis is a rare lung disorder characterised by cystic air spaces and **smooth muscle** proliferation. The condition, which most commonly presents with dyspnoea, pneumothoraces or cough, is only described in females and is most commonly diagnosed during

childbearing years. Three cases are presented which illustrate typical features of the disease and the association with high oestrogen levels. The first had recurrent pneumothoraces during her first pregnancy. The second lady was post menopausal at diagnosis but her symptoms predated her menopause. The third, presented with dyspnoea, abnormal chest sensations and a pneumothorax. She had a history of hyperprolactinaemia with secondary amenorrhoea due to low oestrogen levels which had been corrected prior to her presentation. All three patients had reduced gas transfer and abnormalities in spirometry, two had reticular shadowing on their chest radiograph and all had typical appearances on lung computerised tomography. Although disease progression was variable, all patients showed a gradual decline in lung function.

L74 ANSWER 4 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2001316000 EMBASE The thrombophilic state in cancer patients. Gouin-Thibault I.; Achkar A.; Samama M.M.. M.M. Samama, Serv. d'Hematologie Biologique, Hopital Hotel Dieu, 1 place Parvis Notre Dame, F-75 181 Paris Cedex 04, France. Acta Haematologica 106/1-2 (33-42) 2001.

Refs: 76.

ISSN: 0001-5792. CODEN: ACHAAH. Pub. Country: Switzerland. Language: English. Summary Language: English.

AB Thrombosis and disseminated intravascular coagulation are common complications of cancer. Specific conditions associated with cancer such as stasis due to immobilization or blood flow obstruction, **surgery**, infections, **endothelium damage** due to chemotherapeutic agents and abnormalities of blood coagulation contribute to the hypercoagulable and thrombophilic state of cancer patients. This procoagulant state in cancer arises mostly from the capacity of tumor cells to express and release procoagulant activities (cancer procoagulant and tissue factor). Decreased levels of inhibitors of coagulation, impaired fibrinolysis, the presence of antiphospholipid antibodies and an acquired activated protein C resistance contribute to the hypercoagulable state. The activation of coagulation is also implicated in tumor proliferation through interactions of coagulation with inflammation and increased tissue factor pathway inhibitor. Laboratory diagnosis of the thrombophilic state include (1) elevation of clotting factors, fibrinogen/fibrin degradation products, hyperfibrinogenemia and thrombocytosis and (2) elevation of specific markers of activation of coagulation: fibrinopeptide A, fragment 1 + 2, thrombin-antithrombin complexes and D-dimers. However, none of the tests has any predictive value for the occurrence of thrombotic events in one individual patient. In patients with venous thromboembolism a noninvasive screening for occult cancer is able to detect a relatively high incidence of hidden cancer and the search for thrombophilia seems important in patients without known cancer. Copyright .COPYRG. 2001 S. Karger AG, Basel.

L74 ANSWER 5 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2000142106 EMBASE Estrogen receptors .alpha. and .beta.: Prevalence of estrogen receptor .beta. mRNA in human vascular **smooth muscle** and transcriptional effects. Hodges Y.K.; Tung L.; Yan X.-D.; Graham J.D.; Horwitz K.B.; Horwitz L.D.. Dr. L.D. Horwitz, Cardiology B130, Univ. of Colorado Hlth. Sci. Center, Denver, CO 80262, United States. lawrence.horwitz@UCHSC.edu. Circulation 101/15 (1792-1798) 18 Apr 2000.

Refs: 29.

ISSN: 0009-7322. CODEN: CIRCAZ. Pub. Country: United States. Language: English. Summary Language: English.

AB Background - Estrogens have vascular effects through the activation of estrogen receptors (ERs). In addition to ER.alpha., the first ER to be cloned, a second subtype called ER.beta. has recently been discovered. Methods and Results - Using a reverse-transcriptase polymerase chain reaction assay that employs the same primer pair to simultaneously amplify

ER.alpha. and ER.beta. transcripts, we found that ER.beta. is the ER form that is predominantly expressed in human vascular **smooth muscle**, particularly in women. The transcriptional effects of the 2 ERs in transfected HeLa cells differed. In response to 17.beta.-estradiol, ER.alpha. is a stronger transactivator than ER.beta. at low receptor concentrations. However, at higher receptor concentrations, ER.alpha. activity self-squelches, and ER.beta. is a stronger transactivator. **Tamoxifen** has partial agonist effects with ER.alpha. but not with ER.beta.. Conclusions - The protective effects of estrogens in the cardiovascular system of women may be due to the genomic effects of ER.beta. in vascular tissue.

L74 ANSWER 6 OF 25 MEDLINE

2001059786 Document Number: 20536800. PubMed ID: 11082402. Selective estrogen receptor modulator idoxifene inhibits **smooth muscle** cell proliferation, enhances reendothelialization, and inhibits neointimal formation in vivo after vascular injury. Yue T L; Vickery-Clark L; Loudon C S; Gu J L; Ma X L; Narayanan P K; Li X; Chen J; Storer B; Willette R; Gossett K A; Ohlstein E H. (Department of Cardiovascular Pharmacology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, USA.. Tian-Li_Yue@sbphrd.com) . CIRCULATION, (2000 Nov 7) 102 (19 Suppl 3) III281-8. Journal code: 0147763. ISSN: 1524-4539. Pub. country: United States. Language: English.

AB BACKGROUND: Idoxifene (ID) is a tissue-selective estrogen receptor modulator (SERM). The pharmacological profile of ID in animal studies suggests that it behaves like an estrogen receptor (ER) agonist in bone and lipid metabolism while having negligible ER activity on the reproductive system. It is unknown whether ID retains the vascular protective effects of estrogen. METHODS AND RESULTS: In cultured vascular **smooth muscle** cells (VSMCs), ID inhibited platelet-derived growth factor-induced DNA synthesis and mitogenesis with IC(50) values of 20.4 and 27.5 nmol/L, respectively. Treatment with ID resulted in S-phase cell cycle arrest in serum-stimulated VSMCs. ID 1 to 100 nmol/L significantly protected endothelial cells from tumor necrosis factor-alpha (TNF-alpha)-induced apoptosis in vitro. Virgin Sprague-Dawley rats ovariectomized 1 week before the study were treated with ID (1 mg x kg(-1) x d(-1)) or vehicle by gavage for 3 days before balloon denudation in carotid artery. The SMC proliferation in injured vessels was determined by immunostaining for proliferating cell nuclear antigen (PCNA). The number of PCNA-positive SMCs was reduced by 69%, 82%, and 86% in the media at days 1, 3 and 7, respectively, and by 78% in the neointima at day 7 after injury in ID- versus vehicle-treated group (P:<0.01). ID significantly enhanced reendothelialization in the injured carotid arteries as determined by Evans blue stain and immunohistochemical analysis for von Willebrand factor. In the former assay, the reendothelialized area in injured vessels was 43% in ID-treated group versus 24% in the vehicle group (P:<0.05); in the latter assay, the numbers of von Willebrand factor-positive cells per cross section increased from 24.8 (vehicle) to 60.5 (ID) (P:<0.01) at day 14 after injury. In addition, the production of nitric oxide from excised carotid arteries was significantly higher in ID-treated than the vehicle group (8.5 versus 2.7 nmol/g, P:<0.01). Finally, ID treatment reduced neointimal area and the ratio of intima to media by 45% and 40%, respectively (P:<0.01), at day 14 after balloon angioplasty. CONCLUSIONS: The results indicate that ID beneficially modulates the balloon denudation-induced vascular injury response. Inhibition of VSMC proliferation and acceleration of endothelial recovery likely mediate this protective effect of ID.

L74 ANSWER 7 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2000325578 EMBASE Lymphangioliomyomatosis - Pathology, clinical features, diagnosis and management. Johnson S.; Tattersfield A.E.. S. Johnson,

Division of Therapeutics, University Hospital, Queens Medical Centre,
Nottingham NG57 2UH, United Kingdom. European Respiratory Monograph 5/14
(165-180) 2000.

Refs: 93.

ISSN: 1025-448X. CODEN: EURMF6. Pub. Country: Denmark. Language: English.
Summary Language: English.

- AB Lymphangioleiomyomatosis affects approximately one per million of the population and is restricted to females who are nearly always pre-menopausal. Abnormal **smooth muscle** cells line the airways, lymphatics and blood vessels leading to airflow obstruction and replacement of the lung parenchyma by cysts. Clinically the disease is categorized by dyspnoea, haemoptysis, recurrent pneumothoraces and chylous effusions. The course of the disease is highly variable but is generally progressive, resulting in death from respiratory failure. Lymphangioleiomyomatosis is thought to be hormonally dependent and treatment may include progesterone supplementation or oestrogen depletion. Although none is of proven efficacy, progesterone is probably most likely to be of benefit. Other treatments are supportive and lung transplantation can be used in certain cases. Further research into the aetiology and treatment for lymphangioleiomyomatosis are continuing and will hopefully improve insight into the mechanisms underlying this rare and interesting disease and lead to more definitive treatment.

L74 ANSWER 8 OF 25 HCAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
2000:685939 Document No. 133:348034 Swelling-activated cation channels mediate depolarization of rat cerebrovascular **smooth muscle** by hyposmolarity and intravascular pressure. Welsh, Donald G.; Nelson, Mark T.; Eckman, Delrae M.; Brayden, Joseph E. (Department of Pharmacology, University of Vermont, Burlington, VT, 05405, USA). Journal of Physiology (Cambridge, United Kingdom), 527(1), 139-148 (English) 2000. CODEN: JPHYA7. ISSN: 0022-3751. Publisher: Cambridge University Press.

- AB Increases in intravascular pressure depolarize vascular **smooth muscle** cells. Based on the attenuating effects of Cl⁻ channel antagonists, it has been suggested that swelling-activated Cl⁻ channels may be integral to this response. Consequently, this study tested for the presence of a swelling-activated Cl⁻ conductance in both intact rat cerebral arteries and isolated rat **smooth muscle** cells. A 50 mosmol L⁻¹ hyposmotic challenge (300 to 250 mosmol L⁻¹) constricted rat cerebral arteries. This constriction contained all the salient features of a pressure-induced response including **smooth muscle** cell depolarization and a rise in intracellular Ca²⁺ that was blocked by voltage-operated Ca²⁺ channel antagonists. The hyposmotically induced depolarization was attenuated by DIDS (300 .mu.M) and **tamoxifen** (1 .mu.M), a response consistent with the presence of a swelling-activated Cl⁻ conductance. A swelling-activated current was identified in cerebral vascular **smooth muscle** cells. This current was sensitive to Cl⁻ channel antagonists including DIDS (300 .mu.M), **tamoxifen** (1 .mu.M) and IAA-94 (100 .mu.M). However, contrary to expectations, the reversal potential of this swelling-activated current shifted with the Na⁺ equil. potential and not the Cl⁻ equil. potential, indicating that the swelling-activated current was carried by cations and not anions. The swelling-activated cation current was blocked by Gd³⁺, a cation channel antagonist. Gd³⁺ also blocked both swelling- and pressure-induced depolarization of **smooth muscle** cells in intact cerebral arteries. These findings suggest that swelling- and pressure-induced depolarization arise from the activation of a cation conductance. This current is inhibited by DIDS, **tamoxifen**, IAA-94 and gadolinium.

L74 ANSWER 9 OF 25 MEDLINE DUPLICATE 2
1999450017 Document Number: 99450017. PubMed ID: 10520314. [Intravascular leiomyomatosis of uterine origin. a case of pseudo-metastatic cavo-cardial

thrombus]. Leiomyomatose intravasculaire d'origine uterine. A propos d'un thrombus cavo-cardiaque pseudo-metastatique. Le Bouedec G; Bailly C; Penault-Llorca F; Fonck Y; Dauplat J. (Centre Regional de Lutte Contre le Cancer Jean Perrin, Clermont-Ferrand.) PRESSE MEDICALE, (1999 Sep 18) 28 (27) 1463-5. Ref: 11. Journal code: 8302490. ISSN: 0755-4982. Pub. country: France. Language: French.

AB BACKGROUND: Leiomyomatosis is a benign **smooth muscle** tumor which can provoke serious complications in case of intracaval or intracardiac extension. CASE REPORT: A 61-year-old woman had undergone hysterectomy at the age of 45 years for a hemorrhagic fibroma. She underwent **surgery** for infiltrative breast cancer 3 months before hospitalization and was taking **tamoxifen** 30 mg/day. In the cancer context, the diagnosis of cavo-cardiac metastatic thrombus was proposed but not confirmed at pathology. The diagnosis of uterine tissue intravascular leiomyomatosis was established on the basis of pathology findings and immunohistochemistry results. DISCUSSION: Five other cases of leiomyomatosis after hysterectomy have been reported in the literature.

L74 ANSWER 10 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

1999269926 EMBASE Low-grade endometrial stromal sarcoma with intracardiac extension. Evolution of extensive **smooth muscle** differentiation and usefulness of immunohistochemistry for its recognition and distinction from intravenous leiomyomatosis. Mikami Y.; Demopoulos R.I.; Bector F.; Febre E.F.; Harris M.; Kronzen I.; Scholes J.V.. Dr. J.V. Scholes, Department of Anatomic Pathology, New York University Medical Center, Tisch Hospital, 560 First Avenue, New York, NY 10016, United States. Pathology Research and Practice 195/7 (501-508) 1999. Refs: 33.

ISSN: 0344-0338. CODEN: PARPDS. Pub. Country: Germany. Language: English. Summary Language: English.

AB This case, a rare example of low-grade endometrial stroma sarcoma with extensive **smooth muscle** differentiation which extended to the inferior vena cava and cardiac chambers closely resembling intravenous leiomyomatosis grossly and microscopically, illustrates the importance of extensive sectioning and the usefulness of immunohistochemistry. Although spindle cell components arranged in interlacing bundles consistent with **smooth muscle** differentiation were recognizable in the primary tumor (on retrospective review), extensive **smooth muscle** differentiation in the recurrent tumors masked prototypical morphologic features of stromal sarcoma and only small neoplastic stromal components were preserved in limited areas, leading to initial failure to distinguish the lesion from intravenous leiomyomatosis. The immunophenotyping disclosed two distinct cell populations in the tumor: i.e. vimentin-positive and **smooth muscle** marker negative stromal cells, and vimentin-negative spindle-shaped desmin-positive **smooth muscle** cells. Our observation suggests that the predominance of a **smooth muscle** component in such a tumor can be misleading and does not always warrant a diagnosis of intravenous leiomyomatosis, nor does it predict a benign clinical course. This case also provides an insight into the relationship of the endometrial stroma and myometrium, and their cell of origin and the histogenesis of endometrial stromal sarcoma.

L74 ANSWER 11 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

1999326019 EMBASE Pulmonary lymphangioliomyomatosis: A study of 69 patients. Urban T.; Lazor R.; Lacronique J.; Murris M.; Labrune S.; Valeyre D.; Cordier J.-F.. Prof. J.-F. Cordier, Groupe d'Etudes et de Recherche, Maladies Orphelines Pulmonaires, Hopital Louis Pradel, 69394 Lyon, France. Medicine 78/5 (321-337) 1999. Refs: 90.

ISSN: 0025-7974. CODEN: MEDIAV. Pub. Country: United States. Language: English. Summary Language: English.

AB Pulmonary lymphangiomyomatosis (LAM) is a rare disorder of unknown cause characterized by peribronchial, perivascular, and perilymphatic proliferation of abnormal **smooth muscle** cells leading to cystic lesions. The hypothesis of hormonal dependence and the effectiveness of hormonal therapy have not yet been demonstrated conclusively, and the prevalence of extrathoracic manifestations and the survival of patients with LAM are somewhat contradictory. A multicentric retrospective study was conducted in an attempt to describe better the initial features, the diagnostic procedures, the associated lesions, and, above all, the management and course of LAM in a large homogeneous series of 69 stringently selected patients, with a majority of cases diagnosed since 1990. The aim of the study, based on a review of the literature, also was to provide a comprehensive view of this uncommon disease. The clinical features were in keeping with previous studies, but we found that exertional dyspnea and pneumothorax were the most common features, and chylous involvement was less frequent. LAM was diagnosed after menopause in about 10% of cases. The onset of LAM occurred during pregnancy in 20% of cases, and a clear exacerbation of LAM was observed in 14% of cases during pregnancy. Pulmonary LAM was diagnosed on lung histopathology in 83% of cases, but renal angiomyolipoma, observed in 32% of our patients, may be a useful diagnostic criterion when associated with typical multiple cysts on chest CT scan or with chylous effusion. Chest CT scan was more informative than chest X-ray (normal in 9% of cases), and may be indicated in spontaneous pneumothorax or renal angiomyolipoma in women of childbearing age. About 40% of the patients had a normal initial spirometry, while an obstructive ventilatory defect (44%), a restrictive ventilatory defect (23%), was observed in other patients. Initial diffusing capacity for carbon monoxide was frequently decreased (82%). Hormonal therapy was administered in 57 patients, but a clear .gtoreq. 15% improvement of FEV1 was observed in only 4 evaluable patients, treated with **tamoxifen** and progestogens (n = 2), progestogen (n = 1), and oophorectomy (n = 1). Probably 1 of the most urgent needs for clinical research in LAM is to test the currently available hormonal treatments in the context of international multicenter prospective controlled studies. Pleurodesis was performed in 40 patients. Lung transplantation was performed in 13 patients, 7.8 \pm 5.2 years after onset of LAM, in whom the mean FEV1 was 0.57 \pm 0.15 L. After a follow-up of 2.3 \pm 2.2 years, 9 patients were alive. Mean follow-up from onset of disease to either death or closing date was 8.2 \pm 6.3 years. Overall survival was better than usually reported in LAM, and Kaplan-Meier plot showed survival probabilities of 91% after 5 years, 79% after 10 years, and 71% after 15 years of disease duration.

L74 ANSWER 12 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999207070 EMBASE Postmenopausal hormone replacement, risk estimators for **coronary artery disease** and cardiovascular protection. Mijatovic V.; Van der Mooren M.J.; Stehouwer C.D.A.; Netelenbos J.C.; Kenemans P.. Prof. P. Kenemans, Department Obstetrics and Gynecology, Univ. Hospital Vrije Universiteit, De Boelelaan 1117, 1081 HV Amsterdam, Netherlands. Gynecological Endocrinology 13/2 (130-144) 1999. Refs: 129.
ISSN: 0951-3590. CODEN: GYENER. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Menopause, regardless of age at onset, is associated with a marked increase in **coronary artery disease** (CAD) risk. A large body of observational clinical studies repeatedly demonstrated favorable associations between postmenopausal hormone replacement therapy (HRT) and cardiovascular morbidity, mortality, and risk factors. Estrogens may act in a gender-specific way on vascular endothelial cells and other components of the vessel wall, enhancing the synthesis and release of nitric oxide (NO) and other vasodilators, and by inhibiting the synthesis and release of vasoconstricting agents, thus

favoring vasodilation. Menopause-related changes in metabolic cardiovascular risk factors are identifiable, as are HRT-related changes in these factors. The metabolic effects include changes in lipoprotein (a), coagulation and fibrinolysis as well as homocysteine metabolism. The various actions of estrogen alone and combined with progestogen on the vascular system are reviewed. Furthermore, the outcome of the recently published Heart and estrogen/progestin replacement study (HERS) data are put in perspective. In addition, we outline the present data on the effects of raloxifene, a new second generation selective estrogen receptor modulator (SERM), which has been shown to favourably alter several markers of cardiovascular risk in postmenopausal women.

L74 ANSWER 13 OF 25 HCAPLUS COPYRIGHT 2002 ACS

1998:708808 Document No. 129:310911 TGF-.beta.-elevating compounds and therapies for the prevention of vascular and non-vascular pathologies, and diagnostic methods. Grainger, David J.; Metcalfe, James C.; Kasina, Sudhakar (Neorx Corp., USA). PCT Int. Appl. WO 9846588 A2 19981022, 153 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US7063 19980409. PRIORITY: US 1997-43852 19970411.

AB A method is provided for treating a mammal having, or at risk of, an indication assocd. with a TGF-.beta. deficiency, comprising administering one or more agents that is effective to elevate the level of TGF-.beta.. The invention also provides compds. that elevate TGF-beta levels, as well as pharmaceutical compns. comprising compds. that elevate TGF-beta levels and methods for detecting diseases assocd. with endothelial cell activation.

L74 ANSWER 14 OF 25 HCAPLUS COPYRIGHT 2002 ACS

1998:788752 Document No. 130:33027 TGF-.beta. activators and TGF-.beta. production stimulators for prevention and treatment of pathologies associated with abnormally proliferative **smooth muscle** cells. Grainger, David J.; Metcalfe, James C.; Weissberg, Peter L. (NeoRx Corporation, USA). U.S. US 5847007 A 19981208, 25 pp., Cont.-in-part of U.S. Ser. No. 61,714, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1994-242161 19940512. PRIORITY: US 1993-61714 19930513.

AB TGF-.beta. activators and TGF-.beta. prodn. stimulators are employed to maintain or increase vessel lumen diam. in a diseased or injured vessel of a mammal. Conditions such as restenosis following angioplasty, vascular bypass grafts, transplanted organs, atherosclerosis or **hypertension** are characterized by a reduced vessel lumen diam. In a preferred embodiment of the invention, TGF-.beta. activators and prodn. stimulators inhibit abnormal proliferation of **smooth muscle** cells. TGF-.beta. activators or prodn. stimulators that are not characterized by an undesirable systemic toxicity profile at a prophylactic dose are also amenable to chronic use for prophylactic purposes with respect to disease states involving proliferation and/or migration of vascular **smooth muscle** cells over time. Further provided is a method for detg. TGF-.beta. in vitro, thereby identifying a patient at risk for atherosclerosis and monitoring a recipient that has received one or more administrations of a TGF-.beta. activator or prodn. stimulator.

L74 ANSWER 15 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

1998323743 EMBASE Catamenial fevers associated with a uterine **smooth muscle** tumor of undetermined malignant potential. Wong A.W.; Leiserowitz G.S.; McCausland V.M.; McCausland A.M.. Dr. A.W. Wong, Dept.

of Obstetrics and Gynecology, University of California, Davis Medical Center, 1621 Alhambra Boulevard, Sacramento, CA 95816, United States. agwong@ucdavis.edu. Obstetrics and Gynecology 92/4 II SUPPL. (671-672) 1998.

Refs: 7.

ISSN: 0029-7844. CODEN: OBGNAS.

Publisher Ident.: S 0029-7844(98)00107-0. Pub. Country: United States.

Language: English. Summary Language: English.

- AB Background: Pyrexia associated with solid and hematogenous neoplasms are a well-recognized clinical condition. Menstrually related (catamenial) fevers have not been reported previously. Case: A 52-year-old woman with a history of stage I breast cancer on adjuvant **tamoxifen** citrate presented with recurrent fevers associated with menses. An extensive evaluation of possible causes, including recurrent breast cancer and infectious, collagen-vascular, and drug-related sources, initially was unrevealing. A gynecologic evaluation identified a uterine tumor, which appeared to be a cellular leiomyoma on hysteroscopic biopsy. The catamenial fevers resolved immediately after hysterectomy. A uterine **smooth muscle** tumor of undetermined malignant potential was identified on pathology. Conclusion: **Smooth muscle** tumors of the myometria are a rare cause of menstrual fevers.

L74 ANSWER 16 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

1998156427 EMBASE Malignant adenomyoepithelioma of the breast with mixed osteogenic, spindle cell, and carcinomatous differentiation. Simpson R.H.W.; Cope N.; Skalova A.; Michal M.. Dr. R.H.W. Simpson, Postgrad. Med. School (Exeter Univ.), Barrack Road, Exeter, Devonshire EX2 5DW, United Kingdom. American Journal of Surgical Pathology 22/5 (631-636) 1998.

Refs: 33.

ISSN: 0147-5185. CODEN: AJSPDX. Pub. Country: United States. Language: English. Summary Language: English.

- AB A 50-year-old woman had a malignant tumor of the left breast, which recurred twice, metastasized, and caused death after 39 months. Histologically, the original neoplasm and the first recurrence comprised an adenomyoepithelioma, in addition to a sarcoma composed of trabeculae of mature and immature bone, osteoid, and partly calcified, dense collagenous tissue. The trabeculae were lined by alpha-**smooth muscle** actin-positive mononuclear tumor cells, which also extended into the stroma. Similarly, scattered osteoclastlike, multinucleate giant cells were present in the stroma and in the region of the trabeculae. This same pattern of adenomyoepithelioma and osteosarcoma also was seen in the last recurrence, together with a proliferation of undifferentiated malignant spindle-shaped cells. The last biopsy also contained a separate small focus of invasive ductal carcinoma of usual type. It was concluded that this, apparently unique, tumor probably represented an adenomyoepithelioma in which a metaplastic sarcoma of osteogenic and undifferentiated types developed from the myoepithelial element, and in which a carcinoma developed from the epithelial component.

L74 ANSWER 17 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

1998199472 EMBASE Endometrial stromal sarcoma with sex cord-like differentiation associated with **tamoxifen** therapy. Pang L.-C.. Dr. L.-C. Pang, Department of Pathology, Chang Gung Hosp. and Medical College, Taipei, Taiwan, Province of China. Southern Medical Journal 91/6 (592-594) 1998.

Refs: 5.

ISSN: 0038-4348. CODEN: SMJOAV. Pub. Country: United States. Language: English. Summary Language: English.

- AB Low-grade endometrial stromal sarcoma with sex cord-like differentiation occurred in two postmenopausal patients who had received **tamoxifen** for more than 3 years after surgical resection for breast cancer. Uterine sarcomas have been described in association with the use of

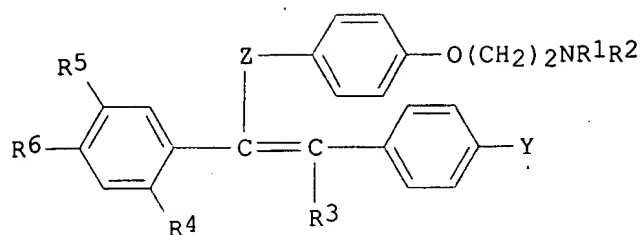
tamoxifen. Only two cases of endometrial stromal sarcoma with sex cord-like features associated with **tamoxifen** use have been reported previously. This report adds an additional two cases of this tumor. Immunohistochemical and ultrastructural examinations of the tumor support the concept of **smooth muscle** differentiation in the sex cord-like areas. This observation proposes that the low-grade endometrial stromal sarcoma with sex cord-like elements may be a consequence of **tamoxifen** ingestion, but the exact mechanism of **tamoxifen** in the development of thin tumor remains speculative.

L74 ANSWER 18 OF 25 MEDLINE DUPLICATE 3
 1998114101 Document Number: 98114101. PubMed ID: 9453356.
 17Beta-estradiol, its metabolites, and progesterone inhibit cardiac fibroblast growth. Dubey R K; Gillespie D G; Jackson E K; Keller P J. (Department of Medicine, University of Pittsburgh Medical Center, PA 15213-2582, USA.. dubey@med1.dept-med.pitt.edu) . HYPERTENSION, (1998 Jan) 31 (1 Pt 2) 522-8. Journal code: 7906255. ISSN: 0194-911X. Pub. country: United States. Language: English.

AB Postmenopausal women (PMW) have increased incidence of cardiovascular disease, and estrogen substitution therapy has been shown to have cardioprotective effects. Since abnormal growth of cardiac fibroblasts (CFs) is associated with **hypertension** and myocardial infarction and estrogen inhibits vascular **smooth muscle** cell (SMC) growth, it is feasible that estrogen may attenuate cardiac remodeling by inhibiting CF growth, and this possibility was investigated by using cultured CFs. 17Beta-estradiol and progesterone, but not 17alpha-estradiol, estrone, or estriol, inhibited 2.5% FCS-induced proliferation (DNA synthesis and cell number) and collagen synthesis (3H-proline incorporation) in a concentration-dependent manner and to a similar extent in male and female CFs. Compared to 17beta-estradiol, its metabolites 2-hydroxyestradiol and 2-methoxyestradiol were more potent in inhibiting FCS-induced DNA synthesis, collagen synthesis, and cell proliferation. The inhibitory effects of 17beta-estradiol and its metabolites were enhanced in presence of progesterone and 4-hydroxytamoxifen (high-affinity estrogen receptor ligand). Moreover, like estrogens, the dietary phytoestrogens biochanin A and daidzein inhibited FCS-induced growth of CFs. In conclusion, 17beta-estradiol, its metabolites, and progesterone inhibit CF growth in a gender-independent fashion. Moreover, hormone replacement therapy using 17beta-estradiol and progesterone may protect PMW against cardiovascular disease by inhibiting CF growth and cardiac remodeling; whereas estrogens that do not inhibit CF growth may be less effective in protecting PMW against cardiovascular disease. Finally, our studies provide evidence that phytoestrogens inhibit CF growth and may be clinically useful as a substitute for feminizing estrogens in preventing cardiovascular disease in both women and men.

L74 ANSWER 19 OF 25 HCAPLUS COPYRIGHT 2002 ACS
 1997:134850 Document No. 126:139887 Prevention and treatment of cardiovascular pathologies with **tamoxifen** analogs. Grainger, David J.; Metcalfe, James C.; Kunz, Lawrence L.; Kemp, Paul R.; Schroff, Robert W.; Weissberg, Peter L. (Neorx Corporation, USA; Grainger, David J.; Metcalfe, James C.; Kunz, Lawrence L.; Kemp, Paul R.; Schroff, Robert W.; Weissberg, Peter L.). PCT Int. Appl. WO 9640098 A2 19961219, 130 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US10211 19960607. PRIORITY: US 1995-478936 19950607; US 1995-476735 19950607; US 1995-477393 19950607; US 1995-486334 19950607.

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AB A method for treating or preventing cardiovascular pathologies comprises administering a compd. I (Z = C:O, covalent bond; Y = H, O(C1-4)alkyl; R1, R2 = (C1-4)alkyl, together with N satd. heterocyclic group; R3 = Et, chloroethyl; R4 = H; R5 = I, O(C1-4)alkyl, H; R6 = I, O(C1-C4)alkyl, H, with the proviso that when R4, R5, and R6 are H, R3 is not ethyl) or a pharmaceutically acceptable salt thereof, effective to elevate the level of TGF- β . to treat and/or prevent conditions such as atherosclerosis, thrombosis, myocardial infarction, and stroke is provided. Useful compds. include idoxifene, raloxifene, toremifene, droloxifene or salts thereof. A method for identifying an agent that elevates the level of TGF- β and an assay or kit to det. TGF- β . based on anti-TGF- β -antibodies are also provided. **Tamoxifen** (1.1 mg/kg/day) strongly inhibited the formation of lipid lesions induced by a high fat diet in mice. The major effect of **tamoxifen** in mice was to elevate TGF- β . in aortic wall and in circulation.

L74 ANSWER 20 OF 25 MEDLINE DUPLICATE 4
 96201114 Document Number: 96201114. PubMed ID: 8618404. Leiomyoma of the breast. Kaufman H L; Hirsch E F. (Department of Surgery, Boston City Hospital, MA 02118, USA.) JOURNAL OF SURGICAL ONCOLOGY, (1996 May) 62 (1) 62-4. Journal code: 0222643. ISSN: 0022-4790. Pub. country: United States. Language: English.

AB Leiomyoma is the most uncommon benign neoplasm of the breast. We report a case of a middle-aged woman with a palpable breast mass who underwent excisional biopsy. Pathologic examination revealed a leiomyoma. The clinical characteristics, pathologic findings, and proper management of this lesion are discussed. The tumor is thought to arise from the **smooth muscle** of the endothelium and can be managed similarly to leiomyomas occurring elsewhere. The possible effects of **tamoxifen** on uterine leiomyomas may be of theoretical concern with breast leiomyomas. The recognition of this entity and an understanding of the management of this rare lesion are necessary by all surgeons who perform breast **surgery**.

L74 ANSWER 21 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
 95287279 EMBASE Document No.: 1995287279. Leuprolide acetate and intravascular leiomyomatosis. Tresukosol D.; Kudelka A.P.; Malpica A.; Varma D.G.K.; Edwards C.L.; Kavanagh J.J.. Texas Univ. M. D. Anderson Can. Ctr., Box 39, 1515 Holcombe Boulevard, Houston, TX 77030, United States. Obstetrics and Gynecology 86/4 II SUPPL. (688-692) 1995. ISSN: 0029-7844. CODEN: OBGNAS. Pub. Country: United States. Language: English. Summary Language: English.

AB Background: Intravascular leiomyomatosis is an uncommon uterine tumor characterized by grossly visible intravascular proliferation of benign **smooth muscle**. Based on its role in reducing the size of leiomyomas, leuprolide acetate was given as induction therapy for extensive inoperable intravascular leiomyomatosis. Case: A 44-year-old woman, gravida 1, para 1-0-0-1, presented in July 1992 with abnormal uterine bleeding. Pelvic examination and ultrasonography revealed the presence of a large irregular pelvic mass. At laparotomy, uterine and

bilateral adnexal masses were noted extending up to the pelvic inlet and into the broad and infundibulopelvic ligaments. This tumor was not resectable. Based on histologic and immunoperoxidase studies, the lesion was interpreted as a plexiform epithelioid **smooth-muscle** tumor of uncertain malignant potential. Leuprolide acetate depot therapy (7.5 mg every 4 weeks) was begun in September 1992 and continued for a total of 20 months. Maximal tumor regression was achieved after 9 months. Subsequent reexploration at 20 months revealed a resectable tumor. Resection was accomplished successfully, leaving no apparent residual disease. Conclusion: Leuprolide acetate induced tumor regression and rendered debulking **surgery** feasible in a patient with previously unresectable, widespread, retroperitoneal intravascular leiomyomatosis. Primary hormone therapy may provide alternative therapeutic options for certain cases of intravascular leiomyomatosis.

L74 ANSWER 22 OF 25 HCAPLUS COPYRIGHT 2002 ACS

1995:444167 Document No. 122:205191 Prevention and treatment of pathologies associated with abnormally proliferative **smooth muscle** cells with TGF-.beta. activators. Grainger, David J.; Metcalfe, James C.; Weissberg, Peter L. (NeorX Corp., USA). PCT Int. Appl. WO 9426303 A1 19941124, 65 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US5265 19940512. PRIORITY: US 1993-61714 19930513.

AB TGF-.beta. activators and TGF-.beta. prodn. stimulators are employed to maintain or increase vessel lumen diam. in a diseased or injured vessel of a mammal. Conditions such as restenosis following angioplasty, vascular bypass grafts, transplanted organs, atherosclerosis, or **hypertension** are characterized by a reduced vessel lumen diam. In a preferred embodiment of the invention, TGF-.beta. activators and prodn. stimulators inhibit abnormal proliferation of **smooth muscle** cells. TGF-.beta. activators or prodn. stimulators that are not characterized by an undesirable systemic toxicity profile at a prophylactic dose are also amenable to chronic use for prophylactic purposes with respect to disease states involving proliferation and/or migration of vascular **smooth muscle** cells over time. Further provided is a method for detg. TGF-.beta. in vitro, thereby identifying a patient at risk for atherosclerosis and monitoring a recipient that has received one or more administrations of a TGF-.beta. activator or prodn. stimulator. Effects of **tamoxifen** and heparin on the proliferation of cultured vascular muscle cells and effects of inhibition of TGF-.beta. activation in transgenic apo(o) ice were also demonstrated.

L74 ANSWER 23 OF 25 HCAPLUS COPYRIGHT 2002 ACS

1995:340981 Document No. 122:96515 Therapeutic inhibitor of vascular **smooth muscle** cells. Kunz, Lawrence Leroy; Klein, Richard A.; Reno, John M.; Grainger, David J.; Metcalfe, James C.; Weissberg, Peter L.; Anderson, Peter G. (Neorx Corp., USA). PCT Int. Appl. WO 9426291 A1 19941124 DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US5266 19940512. PRIORITY: US 1993-62451 19930513.

AB Sustained release dosage forms of TGF-beta activators and TGF-beta prodn. stimulators are employed to maintain or increase vessel lumen diam. in a diseased or injured vessel of a mammal. Conditions such as restenosis following angioplasty, vascular bypass grafts, transplanted organs, atherosclerosis or **hypertension** are characterized by a reduced vessel lumen diam. In a preferred embodiment of the invention, TGF-beta activators and prodn. stimulators inhibit abnormal proliferation of **smooth muscle** cells. Free TGF-beta activators or prodn. stimulators that are not characterized by an undesirable systemic toxicity profile at a prophylactic dose may be used in conjunction with the

sustained release dosage forms described herein for prophylactic purposes with respect to disease and trauma states involving proliferation and/or migration of vascular **smooth muscle** cells over time.

- L74 ANSWER 24 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
92326269 EMBASE Document No.: 1992326269. Flushing reactions in the cancer chemotherapy patient: The lists are longer but the strategies are the same. Wilkin J.K.. Department of Medicine, 4731 UHC, Ohio State University, 456 W 10th Ave, Columbus, OH 43210-1282, United States. Archives of Dermatology 128/10 (1387-1389) 1992. ISSN: 0003-987X. CODEN: ARDEAC. Pub. Country: United States. Language: English.
- L74 ANSWER 25 OF 25 JICST-Eplus COPYRIGHT 2002 JST
880470637 A case of diffuse pulmonary hamartoangiomyomatosis.. SHOJIMA TAKESHI; NAGAO KAZUHARU; MATSUDA MASAKAZU; NISHIMURA HARUYOSHI; TAKEGUCHI TOICHIRO; FUKUMOTO KATSUYA; SHIMA KIYOSHI; HIGUCHI SADANOBU; HAMADA TETSUO. Kumamoto Municipal Hospital. Nippon Kyobu Rinsho (Japanese Journal of Chest Diseases). (1988) vol. 47, no. 3, pp. 257-262. Journal Code: Z0382B (Fig. 4, Tbl. 1, Ref. 23) CODEN: 0385-3667; Pub. Country: Japan. Language: Japanese.
- AB A 25 year-old female was admitted to Kumamoto Municipal Hospital due to left pneumothorax. Partial parietal pleurectomy for pneumothorax and open lung biopsy were performed. Diagnosis of pulmonary hamartoangiomyomatosis was histologically established. She was treated with 40mg of **Tamoxifen** orally every day for 1 year and she was freed from symptoms. One year later, she began to suffer from chest pain again. Then, bilateral Oophorectomy was performed. The symptoms have been gradually alleviated until now.(author abst.)

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